General

Guideline Title

ACMG practice guideline: lack of evidence for *MTHFR* polymorphism testing.

Bibliographic Source(s)

Hickey SE, Curry CJ, Toriello HV. ACMG practice guideline: lack of evidence for MTHFR polymorphism testing. Genet Med. 2013 Feb;15(2):153-6. [77 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

American College of Medical Genetics and Genomics (ACMG) Recommendations

- 5,10-methylenetetrahydrofolate reductase (*MTHFR*) polymorphism genotyping should not be ordered as part of the clinical evaluation for thrombophilia or recurrent pregnancy loss.
- *MTHFR* polymorphism genotyping should not be ordered for at-risk family members.
- A clinical geneticist who serves as a consultant for a patient in whom an *MTHFR* polymorphism(s) is found should ensure that the patient has received a thorough and appropriate evaluation for his or her symptoms.
- If the patient is homozygous for the "thermolabile" variant c.665C→T, the geneticist may order a fasting total plasma homocysteine, if not previously ordered, to provide more accurate counseling.
- *MTHFR* status does not change the recommendation that women of childbearing age should take the standard dose of folic acid supplementation to reduce the risk of neural tube defects as per the general population guidelines (Zacho et al., 2011; De Stefano et al., 2000; Institute of Medicine, Food and Nutrition Board, 1998; "Prevention of neural tube," 1991; Czeizel & Dudás, 1992; "Recommendations for the use of folic acid," 1992; Toriello, 2011).

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Thrombophilia

Guideline Category

Assessment of Therapeutic Effectiveness

Counseling

Evaluation

Clinical Specialty

Family Practice

Hematology

Medical Genetics

Obstetrics and Gynecology

Intended Users

Physicians

Guideline Objective(s)

To review the latest evidence on 5,10-methylenetetrahydrofolate reductase (*MTHFR*) polymorphism testing as part of a routine evaluation for thrombophilia

Target Population

Women of childbearing age and patients at risk for thrombophilia

Interventions and Practices Considered

1. 5,10-methylenetetrahydrofolate reductase (*MTHFR*) polymorphism testing (not recommended)
2. Evaluation of symptoms in patients in whom an *MTHFR* polymorphism(s) is found
3. Fasting total plasma homocysteine
4. Folic acid supplementation

Major Outcomes Considered

Not stated

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The guideline authors searched PubMed and the Cochrane Database of Systematic Reviews from January 1995 to the present. In the literature search, priority was given to original research, with highest emphasis on meta-analyses, followed by case-control and cohort studies. The Literature search excluded review articles, case reports, and articles in languages other than English. Bibliographies of articles deemed to be of the highest quality for their specific topic were combed for additional articles that may have been missed by the initial literature search. In addition, the guidelines of other professional bodies on the same, or related, topic were reviewed.

The databases were searched using the following terms: MTHFR, MTHFR polymorphism, MTHFR thermolabile variant, methylenetetrahydrofolate reductase, and hyperhomocysteinemia. Combined searches were done on specific questions of interest including: MTHFR and stroke, MTHFR and recurrent pregnancy loss, MTHFR and venous thromboembolism, and MTHFR and coronary artery disease. The same combined searches were done for hyperhomocysteinemia and stroke, etc.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Not stated

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review

Description of the Methods Used to Analyze the Evidence

The articles were reviewed by the working group who provided expert consensus.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Not stated

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

The final manuscript was reviewed by the American College of Medical Genetics and Genomics (ACMG) Policy & Practice Guideline Committee Members, followed by the Board of Directors, and then opened up for general college membership comment.

Evidence Supporting the Recommendations

References Supporting the Recommendations

Czeizel AE, Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med. 1992 Dec 24;327(26):1832-5. PubMed

De Stefano V, Casorelli I, Rossi E, Zappacosta B, Leone G. Interaction between hyperhomocysteinemia and inherited thrombophilic factors in venous thromboembolism. Semin Thromb Hemost. 2000;26(3):305-11. [32 references] PubMed

Institute of Medicine, Food and Nutrition Board. Dietary reference intakes: thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. Washington (DC): National Academy Press; 1998.

Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group. Lancet. 1991 Jul 20;338(8760):131-7. PubMed

Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. MMWR Recomm Rep. 1992 Sep 11;41(RR-14):1-7. [14 references] PubMed

Toriello HV, Policy and Practice Guideline Committee of the American College of Medical. Policy statement on folic acid and neural tube defects. Genet Med. 2011 Jun;13(6):593-6. PubMed

Zacho J, Yazdanyar S, Bojesen SE, Tybjaerg-Hansen A, Nordestgaard BG. Hyperhomocysteinemia, methylenetetrahydrofolate reductase c.677C>T polymorphism and risk of cancer: cross-sectional and prospective studies and meta-analyses of 75,000 cases and 93,000 controls. Int J Cancer. 2011 Feb 1;128(3):644-52. PubMed

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of 5,10-methylenetetrahydrofolate reductase (*MTHFR*) polymorphism testing in routine evaluation for thrombophilia

Potential Harms

Not stated

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Feb

Guideline Developer(s)

American College of Medical Genetics and Genomics - Professional Association

Source(s) of Funding

American College of Medical Genetics and Genomics

Guideline Committee

Not stated

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

The authors declare no conflict of interest.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the American College of Medical Genetics and Genomics (ACMG) Web site .

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on November 19, 2013.

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